Alosetron: a case study in regulatory capture, or a victory for patients' rights?

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Senior members of the FDA's advisory committee warn of more deaths if alosetron (Lotronex) is relaunched, as a former insider speaks out about the US regulator's close relationship with Big Pharma

Editorial p 555
News p 561

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In April this year, a special joint advisory committee to the United States Food and Drug Administration (FDA) recommended remarketing GlaxoSmithKline's controversial drug for irritable bowel syndrome, alosetron (Lotronex), which was once considered a potential top seller but was voluntarily withdrawn in late 2000 following serious adverse events, including deaths. Because of the drug's modest benefits and major harms, a key condition of the committee's recommendation was the introduction of a "risk management programme." Committee members emphasised during their deliberations that the drug should be prescribed only by doctors who had been trained and certified to use it. They explicitly rejected a weaker company proposal to allow prescribing by doctors who "self attested" to competency.

Just six weeks later, on 7 June, the FDA formally re-approved marketing, but it announced that prescribing would be based on "physician self-attestation of qualifications," not on the more restrictive system of certification proposed by the committee.

Box 1: The Lotronex timeline

16 November 1999—First FDA advisory committee recommends approval of alosetron hydrochloride (Lotronex), a 5-HT_3 receptor antagonist made by GlaxoWellcome.

9 February 2000—FDA approves alosetron for treating women with "diarrhoea-predominant irritable bowel syndrome"

27 June 2000—Second FDA advisory committee meeting discusses mounting toll of serious adverse events, but votes to keep alosetron on the market

1 July 2000—Dr Paul Stolley joins FDA as "senior consultant"

16 November 2000—Dr Paul Stolley is joint author of internal FDA memo on failure of "risk management" strategies to prevent harms and deaths

28 November 2000—GlaxoWellcome and FDA meet; company withdraws alosetron

December 2001—GlaxoSmithKline seeks to re-market alosetron with restrictions

23 April 2002—Third FDA advisory committee recommends re-marketing, with restrictions

7 June 2002—FDA re-approves alosetron, ignores key committee recommendation on eligible prescribers

Summary points

Advisers from the Food and Drug Administration (FDA) warn of more deaths if alosetron (Lotronex) returns to the market later this year

A former FDA insider says the United States regulatory agency has become a servant of the drug industry, citing his experience with alosetron

The FDA and GlaxoSmithKline reject allegations and say decisions on alosetron were motivated by concerns for patients

Reform that would end drug industry funding of FDA reviews is needed

The FDA is not bound to take all the advice of its committees, but in this case several committee members were furious, and at least three privately communicated their concerns. Now, as GlaxoSmithKline moves towards relaunching alosetron in the United States, the advisers have decided to publicly express those concerns, warning that more deaths may occur and the drug may again have to be withdrawn.[1] What happens in the United States is critical to the drug's future because it will determine whether the company pursues approval anywhere else in the world.

One committee member, Dr Brian Strom of the University of Pennsylvania, says the risk management programme announced on 7 June risks becoming a "façade" that might make commercial sense to the company but doesn't make sense in terms of public health. "With alosetron, the risk-benefit ratio is not worth it, unless the use can be restricted to those who really need it and who are likely to benefit from it—which is a very very small group."

GlaxoSmithKline's alosetron has been approved, withdrawn, and now approved again (box 1), and outside critics allege it is a case study in regulatory capture, given that drug companies partly fund the FDA (box 2).[2 3] Now a former insider has decided to speak

publicly about what he believes is unhealthy corporate influence within the agency.

Insider speaks out

Dr Paul Stolley's job when he joined the FDA in July 2000 (box 3) was to look into the post-marketing safety of alosetron, approved for the first time a few months earlier.

A long time supporter of the FDA, after his recent experience Stolley now claims the regulatory agency has become a servant of industry, where dissenting voices are intimidated and ostracised and where scientific debate is repressed. "I think it's a shame how it has fallen down on the job, and Lotronex is a perfect example. The FDA was in partnership with industry. It should have been negotiating, not in partnership. Why was it in partnership? Because it's financially supported by industry."

The Food and Drug Administration's director of the Centre for Drug Evaluation and Research, Dr Janet Woodcock, strongly rejects those allegations; instead, she says that alosetron offers a great example of the difficulties in providing access to a risky drug for those in greatest need. On Stolley himself she told me only this: "It's our responsibility to be dispassionate and not develop emotionally based positions." Despite repeated requests GlaxoSmithKline would not provide an executive for interview, though a spokesperson denied any inappropriate influence over regulatory decision making.

Playing up benefits, playing down harms

The public transcripts of the three official advisory committee hearings on alosetron show a pattern of company representatives framing the disorder in such a way as to maximise its severity and prevalence—playing up the drug's benefits and minimising the risks of serious adverse events and death.[4–6] The same transcripts show FDA staff offering a more sober and comprehensive view of the evidence, but always within a deferential framework that never challenged the company's right to market the drug, despite alarming internal assessments of its dangers.[7]

The nature of irritable bowel syndrome is itself a source of contention, symptoms ranging from mild or transient abdominal pain to chronic and severe disability that can disrupt daily activities. The drug company describes a "significant disease with a large burden of illness for the individual patient"[5] affecting up to 20% of the population,[6] and it has funded the development of educational programmes to "shape" medical opinion about the "disease"[8] as well as celebrity-driven campaigns to influence public opinion.[9] Others estimate prevalence of around 5%, and the FDA says that fewer than 5% of those cases are considered severe.[10] Adding to the uncertain picture, the drug was approved for a subgroup of women with "diarrhoea-predominant" irritable bowel syndrome, even though, "no objective criteria exist for subgrouping of IBS patients."[11]

The two key phase III trials involved around 600 participants each for three months, and found that women within the subgroup improved significantly on the primary outcome measure of relief of abdominal pain and discomfort and also in terms of urgency, stool frequency, and stool consistency.[11] The company describes the drug as "highly efficacious"[5]; some patients say it is a "miracle medicine"[6]; but the FDA refers instead to "modest" benefits, highlighting an effect in the placebo group that brings relief on the primary outcome measure to 40-50% of women, with only a further 10-20% helped by the drug.[5] The independent consumer watchdog Public Citizen describes marginal benefits, and it has accused trial investigators of using graphic techniques "to greatly exaggerate alosetron's efficacy."[12] Serious questions remain as to whether people enrolled in one of the key trials should even have been defined as having a diarrhoea-predominant condition.[4]

Risks and uncertainty

As to risks, almost a third of patients using alosetron experience constipation. Serious adverse events include severe complications of constipation, ischaemic colitis, hospitalisation, surgery, and death. Complications of constipation occur when faeces are impacted so hard within the bowel that the wall perforates, leading to potentially fatal infections in the body cavity. Ischaemic colitis is the interruption of blood flow to the bowel and can resolve without trauma—or can lead to tissue death and life threatening complications.

At the first advisory committee meeting in November 1999 an FDA officer argued that several cases of

Box 2: How drug companies fund the FDA

In 1992, the United States Congress passed the Prescription Drug User Fee Act (PDUFA), requiring companies to pay fees for drug regulation. Drug companies now pay around $300 000 (£192 000; €302 000) to apply for approval of a new drug, as well as an annual fee of around $145 000 for each manufacturing establishment, and a much smaller amount per product. In total the FDA will receive $162m from industry in 2002, almost half the cost of reviewing drugs.

In return the FDA must meet tighter deadlines for review, which it has done, and must improve its "responsiveness to, and communication with, industry sponsors during the early years of drug development."

The FDA website (www.fda.gov) notes that while private funding has enabled an expansion of staff, public funding is apparently not keeping up with cost increases, leading to important shortages in particular areas. "Just one example of an area we have not been able to fund adequately is responding to reports of adverse events related to the use of prescription drugs."

Box 3: Paul Stolley

1968-76 Assistant and associate professor, Johns Hopkins School of Public Health in Baltimore, Maryland

1976-91 Rorer professor of medicine, University of Pennsylvania School of Medicine

1991-99 Chair and professor, Department of Preventive Medicine, University of Maryland School of Medicine

2000-1 Senior consultant, United States Food and Drug Administration

2002 Emeritus professor, University of Maryland, practising physician and part time staff member at Public Citizen

Member, National Academy of Sciences, Institute of Medicine

Former president, American Epidemiological Society and Society for Epidemiologic Research

Former member, Scientific Advisory Committee of the FDA

ischaemic colitis had been seen in the relatively small trials, so the drug posed a risk to about one in 300 women.[4] GlaxoWellcome (as the company was then) argued this side effect was not associated with alosetron (box 4) and said that most of the cases were caused by *Escherichia coli* infection. Because of the discrepancy in explanations, members of the advisory committee were left uncertain about the problem, and a recommendation was made to approve the drug.

Just seven months later, the complication that GlaxoWellcome had dismissed were already so common that a second advisory committee was convened. By June 2000, 16 people had reportedly required hospitalisation, including 7 with severe complications of constipation and 12 with ischaemic colitis, which by now the company conceded was linked to alosetron. Yet it again attempted to minimise the problem of ischaemic colitis by saying the condition was acute, transient, and self limiting,[5] and it said four times that no deaths had occurred. The drug stayed on the market, accompanied by a "medication guide" about its risks, but by September the first deaths were reported.[7]

Paul Stolley starts work

On 1 July 2000, Paul Stolley started with the FDA as a "senior consultant," and within two months he had written to his superiors warning about alosetron. "I made a strong case the drug was pretty well ineffective and dangerous, and suggested withdrawal be an option for consideration," he told me. "I was so alarmed I was looking at adverse event reports daily. I'd say to my colleagues, have a look at this one, and they'd say that's the one you told us about earlier in the week, and I'd say no, that's a new one." On 13 November company officials met with the FDA, but the scientists tracking harms were not able to present their data, apparently because of time constraints. Three days later Stolley and three colleagues sent a 20-page memo to the director of the gastrointestinal division, warning that a "risk management" plan, the option favoured by the company, would not stop the rising toll of "deaths, colectomies, ischemic colitis, and complications of treatment that were never seen previously in the management of irritable bowel syndrome."[7] The memo refuted the company's argument that controlling constipation among patients taking the drug would "manage the risk" of serious adverse events, including ischaemic colitis.

On 28 November the company and the regulator met again. Stolley's notes on the meeting record company officials aggressively attacking the 16 November memo as being "crappy" and full of errors, while senior FDA officials sat by and failed to defend their staff. "What message is this sending to young epidemiologists?" he asks. "In my opinion it is sending the message that we don't argue with drug companies; we listen to their distortions and omissions of evidence and we do nothing about it." Janet Woodcock won't comment on the meeting other than to say, "The FDA wanted to determine a course forward, not to argue the details."

Box 4: GlaxoSmithKline's changing view of the dangers of alosetron

November 1999: "We conclude there is no evidence for a causal relationship between the development of ischemic colitis and alosetron treatment"

June 2000: "Our overall conclusion is that ischemic colitis appears more frequently than at least was recognized by us"; the company emphasised that the harm is "acute, transient and self-limiting"

April 2002: "Our results show that there is a five-fold increase in the risk of developing ischemic colitis in alosetron-treated subjects"

The drug is withdrawn

Faced with mounting harm and an impasse over how to move forward, the company voluntarily withdrew alosetron from the market at the 28 November meeting. Almost immediately, patient groups activated a campaign for the drug's return. The Lotronex Action Group was set up, unconnected to GlaxoWellcome, and began lobbying both the company and the FDA. The International Foundation for Functional Gastrointestinal Disorders, which did have funding from GlaxoWellcome,[13] also pushed for the drug's return. Its president, Ms Nancy Norton, testified at all three advisory committee meetings without revealing her organisation's link to the manufacturer. Asked why not, she says she was not specifically asked, and that the link appears on her foundation's website.

By January 2001 Stolley felt frozen out of discussions about alosetron's future until he got a call from his superior, Janet Woodcock. Rather than the praise he expected for helping to document adverse events, Stolley heard that alosetron was a good drug, as shown by the huge number of patients demanding it. Woodcock blamed him for "brow-beating" colleagues about its risks and said the drug should be back on the market. "They cut my legs off," Stolley remembers painfully, though he was able to walk out in June 2001, six months ahead of schedule. Woodcock won't comment on the discussion other than to reiterate her point about the need for dispassionate behaviour.

According to Stolley, other staff concerned about the drug's harms were also urged to "help get this drug back on the market," and one of the most senior experts on drug safety was explicitly told not to work on alosetron. Internal emails from the time, published elsewhere,[14 15] seem to support Stolley's suspicions of an unhealthy closeness between senior officials at the FDA, including Woodcock, and senior officials at the company. Both the company and Woodcock reject that dealings were unhealthy, and both argue they were motivated by a desire to help patients. "The FDA had to work with the company in order to facilitate the drug's availability," said Woodcock.

The drug is re-approved

When members of the third advisory committee sat down to discuss alosetron in April 2002, there had been 113 reports of serious complications of constipation, 84 of ischaemic colitis, and six of small bowel ischaemia. Altogether this involved more than 100 reports of hospitalisations, 50 cases of surgery, and at least seven deaths assessed as probably linked to the drug[6]—and as FDA staff pointed out, only 1-10% of such events are reported. The company was by now

stating that ischaemic colitis might occur in four out of every 1000 women taking the drug,[6] yet it was still disputing the association with a number of deaths.

Patients, including those with severe irritable bowel syndrome, testified they were prepared to take these risks; yet, as the FDA had previously said, the company seemed not to have included the most severely affected patients in a key trial.[5]

Availability

During the April meeting, the option was raised of keeping alosetron off the market and making it available compassionately to patients in need through clinical trials, but the option was never properly canvassed by FDA presenters, and it was flatly rejected by the company. The FDA had long been pushing for this option, as had the Lotronex Action Group, though the group's co-founder Jeffrey Roberts says he appreciates why the manufacturer rejected it: "We understood it was supposed to be a blockbuster drug, and we understood because of commercial considerations, the company wouldn't support that option."

Instead, the focus was on getting the drug back to the market, via a risk management plan. Yet there was general agreement that no risk factors for the serious adverse event of ischaemic colitis had yet been identified. In fact the manufacturer now contradicted earlier claims that constipation was a warning sign. "Despite a concerted analytical effort, no specific risk factors including constipation … have been identified. In other words, there is no evidence that constipation predisposes IBS patients to ischemic colitis."[6] Hence, as regulatory staff made clear, "potentially everyone who takes Lotronex is at risk"—a risk perhaps as high as 1 in 200 at three months.[6]

To try and smooth these concerns, it was proposed that the dosage be halved and the drug restricted to patients who had not responded to conventional treatment, yet the key trials had not tested alosetron at that dose or in that population. With the caveat that prescribing be restricted to specially certified doctors—a caveat later ignored by the FDA—the committee voted for re-approval.

Warnings

Like other committee members, Paul Stolley now warns of more deaths and another withdrawal, and he remains scathing about the FDA. "It is confused and frightened. It's getting its money from industry now and it's afraid to offend these companies. And remember Big Pharma was one of the biggest contributors to the Bush campaign."

By coincidence, just two weeks after the recent re-approval, GlaxoSmithKline's president of pharmaceutical operations in the United States, Bob Ingram, was reported to have given the toast to President Bush at a fundraiser in Washington, DC, where pharmaceutical companies gave $250 000 in "soft money."[16] Asked about the event, a company spokeswoman said most donations are by employees simply participating in the democratic process, and she denied undue influence on regulatory decisions. She added that it might be Christmas before alosetron is relaunched, and the company was no longer expecting to make a profit on it.

Alosetron is one of eight drugs approved in the United States in the past decade and subsequently withdrawn for safety reasons, and some voices are calling for an end to industry funding of the FDA's drug reviews.[15 17] But it will likely need more insiders than Paul Stolley to speak out about the truth or otherwise of inappropriate corporate influence, and perhaps many more drug related deaths, before such reforms are taken seriously.

STEWART COOK/REX FEATURES

"Frasier" star Kelsey Grammer and his wife Camille launched a public education initiative to raise awareness about irritable bowel syndrome

Quotes from Paul Stolley, Brian Strom, Janet Woodcock, and an unnamed advisory committee member, and paraphrased comments from GlaxoSmithKline spokespeople all come from interviews which RM conducted in August 2002. A specific request for interview with GlaxoSmithKline executive Mr Bob Ingram to discuss a range of areas, including political donations and the Lotronex case, was declined.

Competing interests: None declared.

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